

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
13 July 2000 (13.07.2000)

PCT

(10) International Publication Number
WO 00/40230 A3

- (51) International Patent Classification⁷: A61K 31/565, 31/58, 31/585, 31/567, 31/568, 31/569
- (21) International Application Number: PCT/US00/00096
- (22) International Filing Date: 4 January 2000 (04.01.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 09/226,068 6 January 1999 (06.01.1999) US
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- (81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— With international search report.
— Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.
- (88) Date of publication of the international search report: 17 May 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: HORMONE REPLACEMENT FOR BREAST CANCER PATIENTS

WO 00/40230 A3 (57) Abstract: Disclosed is a method of androgen replacement therapy to maintain or restore a woman's physiologic normality, including her bone density, vasomotor stability, sexual function, and energy. Also described is a method of treating or preventing osteoporosis in women. A woman is administered pharmaceutical compositions, comprising a non-aromatizable androgen, without estradiol or any estrogenic compound, by a route other than the digestive tract, such that 5 to 500 micrograms of the non-aromatizable androgen is administered daily. Pharmaceutical compositions for delivering a non-aromatizable androgen to a woman at higher than normal risk of breast cancer or endometrial cancer, are formulated to deliver an effective dose transdermally, trans-mucosally or by any delivery route, except the digestive tract. Non-aromatizable androgens that are contemplated include, but are not limited to, methyltestosterone, 17-alpha-methyl-19-nor-testosterone, danazol, fluoxymesterone, methandrostenolone, oxandrolone, oxymetholone, stanozolol, and testosterone. But also contemplated among useful non-aromatizable androgens are androgenic progestins, including desogestrel, norgestimate, norethindrone, norethindrone acetate, norgestrel, ethynodiol diacetate and levonorgestrel. The absence from these compositions of estradiol, or any estrogenic compound, such as testosterone, avoids the estrogen exposure which increases the cancer risk. Androgen delivery other than by ingestion permits lower effective doses and thus lowers the risk of virilizing effects and potential liver toxicity than previously available androgen replacement preparations.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/565 A61K31/58 A61K31/585 A61K31/567 A61K31/568
A61K31/569

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 330 786 A (IGARASHI MASAO) 6 September 1989 (1989-09-06) column 1, line 1 -column 2, line 55 column 5, line 57 -column 6, line 23; claims 1-13; examples 1-4 column 9 -column 11, line 40 ---	1
X	EP 0 474 374 A (ORTHO PHARMA CORP) 11 March 1992 (1992-03-11) abstract page 1, line 7-9 page 1, line 52 -page 4, line 58; claims 1-8; examples 1-5; table 1 --- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"B" document member of the same patent family

Date of the actual completion of the international search

8 September 2000

Date of mailing of the international search report

23.03.01

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/00096

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 44 05 899 A (SCHERING AG) 24 August 1995 (1995-08-24) abstract column 1, line 35-39 column 1, line 61-67 column 4, line 59 -column 5, line 8 column 5, line 25-53 claims 5,6; examples 1,2 ---	1
X	EP 0 587 047 A (JENAPHARM GMBH) 16 March 1994 (1994-03-16) page 1, line 1-7 page 3, line 10-22; claims 6,7; examples 2,3 ---	1
X	WARNOCK JULIA JILL K ET AL: "Female hypoactive sexual desire disorder due to androgen deficiency: Clinical and psychometric issues." PSYCHOPHARMACOLOGY BULLETIN, vol. 33, no. 4, 1997, pages 761-766, XP000934033 ISSN: 0048-5764 abstract page 763, column 1 -page 764, column 1 ---	1-3,5-9, 12-14, 16-20, 23-25, 27-31, 34-37, 39-45, 47-51
X	SCHENNETTEN F ET AL: "[Therapy of the postmenopausal osteoporosis using methyltestosterone plus ergocalciferol or methylandrostenedione]. Zur Therapie der postmenopausischen Osteoporose mit Methyltestosteron plus Ergocalciferol oder Methylandrosteniol." MEDIZINISCHE WELT, (1976 FEB 27) 27 (9) 444-5., XP000934087 page 445, column 1, paragraph 2 -column 2, paragraph 2 ---	1-3,5-9, 12-14, 16-20, 23-25, 27-31, 34-37, 39-45, 47-51
X	PERJU A ET AL: "THE PHARMACOKINETICS OF METHYLTESTOSTERONE ADMINISTERED IN TABLET FORM IN A SINGLE INTRAVAGINAL DOSE AND CLINICAL EVALUATION IN SOME GYNECOLOGICAL AND SENOLOGICAL INVOLVEMENTS" REVISTA DE PEDIATRIE OBSTETRICA SI GINECOLOGIE SERIA OBSTETRICA SI, vol. 35, no. 1, 1987, pages 67-75, XP000934116 1987 ISSN: 0377-4961 the whole document ---	1-3,5-9, 12-14, 16-20, 23-25, 27-31, 34-37, 39-45, 47-51

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INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/US 00/00096

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RECKER R R ET AL: "EFFECT OF ESTROGENS AND CALCIUM CARBONATE ON BONE LOSS IN POST MENOPAUSAL WOMEN" ANNALS OF INTERNAL MEDICINE, vol. 87, no. 6, 1977, pages 649-655, XP000934160 EN ISSN: 0003-4819 abstract page 649, column 2, paragraph 3 -page 650, column 1, paragraph 1; tables 1,3 ---	1-3,5-9, 12-14, 16-20, 23-25, 27-31, 34-37, 39-45, 47-51
X	OEHLERT G.: "[Treatment of disturbances of sexual function in women using ovulation inhibitors]. BEOBACHTUNGEN BEI DER BEHANDLUNG SEXUELLER FUNKTIONSTORUNGEN DER FRAU WAHREND DER EINNAHME VON OVULATIONSHEMMERN." Z.ALLG.MED., (1974) 50/31 (1414-1416). CODEN: ZACMAH, XP000934196 page 1414, column 3, paragraph 2 -page 1415, column 3, paragraph 1; table 1 ---	1-3,5-9, 12-14, 16-20, 23-25, 27-31, 34-37, 39-45, 47-51
X	RAISZ LAWRENCE G ET AL: "Comparison of the effects of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women." JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 81, no. 1, 1996, pages 37-43, XP000934187 ISSN: 0021-972X abstract page 38, column 1, paragraph 2 ---	1-3,5-9, 12-14, 16-20, 23-25, 27-31, 34-37, 39-45, 47-51
X	DAVIS S.R.: "The clinical use of androgens in female sexual disorders." JOURNAL OF SEX AND MARITAL THERAPY, (1998) 24/3 (153-163)., XP000934164 the whole document --- -/--	1-3,5-9, 12-14, 16-20, 23-25, 27-31, 34-37, 39-45, 47-51

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/US 00/00096

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WATTS NELSON B ET AL: "Comparison of Oral Estrogens and Estrogens Plus Androgen on Bone Mineral Density, Menopausal Symptoms and Lipid-Lipoprotein Profiles in Surgical Menopause." OBSTETRICS & GYNECOLOGY, vol. 85, no. 4, 1995, pages 529-537, XP000934017 ISSN: 0029-7844 abstract ---	1-3,5-9, 12-14, 16-20, 23-25, 27-31, 34-37, 39-45, 47-51
X	MYERS L S ET AL: "Effects of estrogen, androgen, and progestin on sexual psychophysiology and behavior in postmenopausal women." JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, (1990 APR) 70 (4) 1124-31., XP000861804 abstract ---	34-37, 39-45, 47-51
X	WO 98 32465 A (LG CHEMICAL LIMITED ;CHOI JONG KUN (KR); CHOI MI SUK (KR); MOON CH) 30 July 1998 (1998-07-30) page 4, line 21-36 -----	34-37, 39-45, 47-51

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

See extra sheet. Invention 1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3,5-9,12,14,16-20,23-25,27-31,34-37,
39-45 (all partially), 13,47-51

Use of 17-alpha-methyl-testosterone to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising 17-alpha-methyl-testosterone.

2. Claims: 1,3,5-9,12,14,16-20,23-25,27-31,34-37,
39-45 (all partially)

Use of 17-alpha-methyl-19-nortestosterone to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising 17-alpha-methyl-19-nortestosterone.

3. Claims: 1,3,5-9,12,14,16-20,23-25,27-31,34-37,
39-45 (all partially)

Use of danazol to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising danazol.

4. Claims: 1,3,5-9,12,14,16-20,23-25,27-31,34-37,
39-45 (all partially)

Use of fluoxymesterone to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising fluoxymesterone.

5. Claims: 1,3,5-9,12,14,16-20,23-25,27-31,34-37,
39-45 (all partially)

Use of methandrostenolone to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising methandrostenolone.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

6. Claims: 1,3,5-9,12,14,16-20,23-25,27-31,34-37,
39-45 (all partially)

Use of oxandrolone to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising oxandrolone.

7. Claims: 1,3,5-9,12,14,16-20,23-25,27-31,34-37,
39-45 (all partially)

Use of oxymetholone to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising oxymetholone.

8. Claims: 1,3,4-9,12,14,16-20,23-25,27-31,34-37,
39-45 (all partially), 4,15,26,38

Use of stanozolol and 5-alpha reduced dihydrotestosterone (stanozolone) to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising stanozolol and 5-alpha reduced dihydrotestosterone (stanozolone).

9. Claims: 1,3,5-9,12,14,16-20,23-25,27-31,34-37,39-45,
(all partially)

Use of testolactone to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising testolactone.

10. Claims: 1,10,12,21,23,27-32,34,46 (all partially)

Use of desogestrel to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising desogestrel.

11. Claims: 1,10,12,21,23,27-32,34,46 (all partially)

Use of norgestimate to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

pharmaceutical compositions comprising norgestimate.

12. Claims: 1,10,12,21,23,27-32,34,46 (all partially)

Use of norethindrone or norethindrone acetate to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising norethindrone or norethindrone acetate.

13. Claims: 1,10,12,21,23,27-32,34,46 (all partially), 11,22,33

Use of norgestrel or levonorgestrel to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising norgestrel or levonorgestrel.

14. Claims: 1,10,12,21,23,27-32,34,46 (all partially)

Use of ethynodiol diacetate to maintain or restore a woman's physiologic normality, provide for androgen replacement therapy and to treat or prevent osteoporosis and pharmaceutical compositions comprising ethynodiol diacetate.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 3.

Although claims 1-33 are directed to a method of treatment of the human/animal -body, the search for the first invention has been carried out and based on the alleged effects of the pound/composition.

Further defect(s) under Article 17(2)(a):

Continuation of Box 3.

Present claims 1,5-9,12,16-20,23,27-31,34,35,39,48-51 relate to a therapeutic application/pharmaceutical composition defined by reference to the following parameter(s):
P1: (synthetic) non-aromatizable androgen/estrogenic compound.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search for the first invention has been restricted to the therapeutic use of 17-alpha-methyltestosterone in relation to the restoration of a woman's physiologic normality (androgen replacement therapy, treatment or prevention of osteoporosis) by a delivery route other than the digestive tract.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/00096

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
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